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JC02 Rec'd PCT/PTO 29 MAR 2002

FORM PTO-1390 (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 01243.000001

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5): 10/089439

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/ZA00/00180	September 29, 2000	September 29, 1999

TITLE OF INVENTION

A SLOW RELEASE PHARMACEUTICAL COMPOSITION

APPLICANT(S) FOR DO/EO/US

HENRY JOHN DAVIS

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2)) (English)
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 into English (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 into English (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern other document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information: PCT Notification of Transmittal of the International Preliminary Examination Report (PCT Rule 71.1); Application Data Sheet; PCT International Preliminary Examination Report (PCT Article 36 and Rule 70) with Annexes, all in English originally.

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 10/089439	INTERNATIONAL APPLICATION NO. PCT/ZA00/00180	JC10 Rec'd PCT/PTO 29 MAR 2002 ATTORNEY'S DOCKET NUMBER 01243.000001

21. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5):		
Search Report has been prepared by the EP or JPO **$890.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492(a)(1)) **$710.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a)(1)) but international search fee paid to USPTO (37 CFR 1.492(a)(2)) **$740.00**		
Neither international preliminary examination fee (37 CFR 1.492(a)(1)) nor international search fee (37 CFR 1.492(a)(2)) paid to USPTO **$1,040.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a)(4)) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	17-20 =	0	X **$18.00**	$ -0-	
Independent Claims	2-3 =	0	X **$84.00**	$ -0-	
Multiple dependent claim(s) (if applicable)			+ **$280.00**	$ 280.00	
			TOTAL OF ABOVE CALCULATIONS =	$1170.00	
☒ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$ 585.00	
			SUBTOTAL =	$ 585.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
			TOTAL NATIONAL FEE =	$ 585.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
			TOTAL FEES ENCLOSED =	$ 585.00	
				Amount to be:	
				refunded	$
				charged	$

a. ☒ A check in the amount of $ 585.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1205. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: (Cust. No. 05514)

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SIGNATURE

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38,586
REGISTRATION NUMBER

249129v1

Application Data Sheet

Application Information

Application Type::	Utility
CD_ROM or CD-R?::	None
Number of CD disk::	0
Number of copies of CDs::	0
Number of copies of CRF::	0
Title::	A SLOW RELEASE PHARMACEUTICAL COMPOSITION
Attorney Docket Number::	01243.000001
Total Drawing Sheets::	0
Small Entity?::	Yes

Applicant Information

Primary Citizenship Country::	South Africa
Status::	Full Capacity
Given Name::	Henry
Family Name::	Davis
City of Residence::	George
Country of Residence::	Republic of South Africa

Correspondence Information

Correspondence Customer Number::	5514

Representative Information

Representative Customer Number::	05514

Foreign Priority Information

Country::	Application Number::	Filing Date::	Priority Claimed:
South Africa	99/6190	09/29/1999	Yes
PCT	PCT/ZA00/00180	09/29/2000	Yes

Initial 3/28/02

01243.000001

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	:	Examiner: N/Y/A
JOHN HENRY DAVIS	)	
	:	Group Art Unit: N/Y/A
Application No.: N/Y/A	)	
	:	
Filed: Herewith	)	
	:	
For: A SLOW RELEASE PHARMACEUTICAL COMPOSITION	)	March 28, 2002

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to examination, please amend the above-identified application as follows:

IN THE SPECIFICATION:

In the first sentence after the title, please amend the specification so as to add the following paragraph:

--This application is filed under 35 U.S.C. § 371. Applicant hereby claims priority under the international Convention and all rights to which he is entitled under 35 U.S.C. § 119 based upon International Application No.

PCT/ZA00/00180, filed September 29, 2000, published in English as International Publication No. WO 01/22943 A1, and based upon South African Application 99/6190, filed September 29, 1999, from which benefit also is claimed.--

REMARKS

This is a national stage application based upon International Application No. PCT/ZA00/00180, filed September 29, 2000, and which claims priority from South African Application 99/6190, filed September 29, 1999. The specification has been amended to recite the required reference to the prior International Application to which benefit is claimed, in accordance with 37 C.F.R. § 1.78.

An early and favorable action on the merits is respectfully requested.

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

Joseph W. Ragusa

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NY_MAIN 248898 v 1

A SLOW RELEASE PHARMACEUTICAL COMPOSITION

FIELD OF THE INVENTION:

This invention relates to slow release pharmaceutical compositions. More particularly it relates to the combination of hygroscopic solid, liquid or gaseous pharmaceutically active substances with solidifying materials thereby to produce solid compositions which, when taken orally, has slow releasing properties in respect of the substance so incorporated into the composition.

BACKGROUND TO THE INVENTION:

It is known that magnesium chloride hexahydrate and L-carnitine base are both recommended dietary supplements for a variety of indications.

The main function of carnitine in the human body is to help in the transport of long chain fatty acids. These fatty acids are utilized inside cells to provide energy. This is a major source of muscular energy. Thus carnitine is used in health supplements to boost energy, prevent fatigue, and maintain the body. Carnitine also increases the use of fat as an energy source thus preventing fat buildup in the heart, liver, and muscles. By doing so carnitine reduces poor metabolism health problems like diabetes, high tri-glyceride blood levels, obesity, weak muscles, and heart disorders. Carnitine has the added

benefit that it increases the effects of the anti-oxidants vitamin E and vitamin C. Carnitine supplementation has become very popular and the most common supplemental forms include L-carnitine, DL-carnitine, and acetyl-L-carnitine.

The applicant considers the concomitant supplemental intake of magnesium and L-carnitine to be desirable in, and beneficial for a number of patient groups whose bodies are considered to be under extraordinary physiological demand, leading to the development of L-carnitine and magnesium deficiency. These groups include (a) women in general in view of their hormonal fluctuations, but in particular those women having demanding lifestyles resulting from workplace and household responsibilities; (b) school going children, and particularly those in puberty; (c) sports people, and in particular those participating in competitive sport for whom the regular supplementation of these products contribute to the reduction, or even the prevention of, lactic acid build up, and furthermore enables the body to produce ATP when needed; (d) the chronically ill or compromised such as, for example, patients suffering from AIDS and undergoing treatment with anti-viral medication where it is known that the ailment and/or the treatment leads to L-carnitine deficiency.

It is known that magnesium chloride hexahydrate and L-carnitine base are hygroscopic on their own. They are even more so when mixed together. It

separately, let alone together in the most desirable dosage form, namely as a dry, solid preparation, e.g. in tablet, capsule or granule form. They are presently being administrated together as a liquid compound. This liquid formulation is not generally considered to be user friendly, and hence conducive to patient compliance, as it has an unpleasant taste and has to be diluted in other liquids.

GB 2 123 693 discloses sustained release devices in which at least one trace chemical element is incorporated in a cement to be releasable therefrom on contact with an aqueous medium. The disclosed cement may comprise magnesium oxychloride and the possibility of incorporating pharmaceuticals is mentioned. No disclosure is however made of the possibility of incorporating a highly hygroscopic substance such as L-carnitine and the like into such a cement for the production of a solid dosage form thereof, or for incorporating a water soluble pharmaceutically active gas, such as nitrous oxide in such a magnesium oxychloride cement.

EU 357 327 discloses the incorporation of the drug amprolium in a magnesium oxysulphate (MOS) cement and the release characteristics of that formulation. It would appear that the cement is in one instance, namely on p 4 line 64 by error referred to as being magnesium oxychloride.

OBJECTS OF THE INVENTION:

To address the above problems, the present invention proposes, and is based upon, the hitherto unknown utilization of a method which, although known as such as a method of solidifying magnesium chloride hexahydrate, has, as far as the applicant is aware, not yet been suggested for use in the manner proposed herein for the preparation of the slow- or sustained release preparations of any one of the wide range of pharmaceutically beneficial

products, including, but not limited to L-carnitine, which may be incorporated into the solid composition as proposed by the present invention.

It is accordingly an object of the present invention to provide a solid, slow release dosage form of a pharmaceutically active substance or combination of substances, and specifically, though not exclusively, of a substance or combination of substances which is hygroscopic, or which is a liquid which contains or is soluble in water, such as, for example, the compound L-carnitine, alcohol and nitrous oxide gas.

PRIOR ART TO THE INVENTION:

The aforementioned known method of converting magnesium chloride into a hard solid composition involves the formation of a so-called Sorel cement (sometimes written as Sorel's cement, and which is also known as magnesium oxychloride cement). It is made by mixing a saturated solution of magnesium chloride with magnesium oxide powder. The resulting paste sets with time to a hard marble like mass. It has the chemical composition represented by $MgCl_2.5MgO.H_20$. Sorel cement is used *inter alia* as dental filling, for the making of floor coverings and laboratory work places, for the preparation of magnesia compounds and in the lubrication of cotton threads for spinning. It is further known that Sorel cement may be mixed with sawdust or cork waste to produce a weatherproof wood like material called xitolite.

The applicant is not aware of any suggestion to use a Sorel cement as a carrier for a pharmaceutically active substance in a slow release preparation.

The reaction to produce Sorel cement is as follows:

$MgCl_2.6H_20 + 5MgO \rightarrow MgCl_2.5MgO.H_20 + 5H_20$.

The stoichiometry of this reaction indicates that the ideal mass ratio of $MgCl_2.6H_20$: MgO is 202 : 200, that is equal masses for all practical purposes. However in the present application for the entrapment of hygroscopic substances in a Sorel cement, it is preferable to use these ingredients in a ratio which presents an excess of MgO, i.e. preferably in a mass ratio of 0,99 $MgCl_2.6H_20$ to 1,25 MgO.

GENERAL DESCRIPTION OF THE INVENTION:

It has now unexpectedly been found that pharmaceutically active substances, such as the L-carnitine base was capable of being "dried" out by being incorporated into a Sorel cement and that it was acceptably stable in that form in the sense that it did not attract water during subsequent handling, such as during encapsulation.

It was also unexpectedly found that the L-carnitine so entrapped in the solid Sorel cement was released from the solid composition when taken into the body by being given orally, even though the compound, while entrapped in the solid composition, was insoluble in ordinary water.

It was also unexpectedly found that the solid composition released the L-carnitine over time and that this was thus suitable as a slow release composition or carrier medium.

It was further unexpectedly found that that a range of solid, particularly hygroscopic solid substances, as well as liquid substances which contain water such as the alcohols and in particular ethyl alcohol could be "dried" out and formulated into a solid composition by this method.

It was also unexpectedly found that gasses which are soluble in water, or in water containing liquids, could be trapped in Sorel cement to be released in the stomach upon being administered orally in the solid dosage form in issue.

Accordingly, the present invention provides a solid dosage form of a pharmaceutically active substance comprising a magnesium oxychloride cement (also known as Sorel cement) in which the pharmaceutically active substance is entrapped.

The solid dosage form may be a powder packed in a capsule.

Alternatively it may be in a compressed tablet form.

The magnesium oxychloride cement of the present invention is preferably made up by mixing a clear magnesium chloride solution containing the pharmaceutically active substance with magnesium oxide powder to form a paste which is then allowed to set over time into a solid composition, which composition is then crushed and milled to the desired fineness.

The pharmaceutically active ingredient is preferably a solid substance selected from the group consisting of L-carnitine, pantothenic acid, pyruvate and combinations thereof.

The pharmaceutically active ingredient may alternatively be a liquid substance such as ethyl alcohol (ethanol).

The pharmaceutically active substance may further alternatively be a gaseous substance which is soluble in water, such as, for example, nitrous oxide.

Without wishing to be bound by this theory, it is the applicant's view that since L-carnitine base is a polar molecule, this polarity attracts a lot of water and is the reason for its extreme hygroscopicity. The molecular water of the L-carnitine base is believed to be taken up during the magnesia (Sorel) cement reaction and both the molecular water and the L-carnitine base is solidified in the cement.

This is also believed to apply in the case of ethanol alone or in combination of L-carnitine with magnesium chloride and magnesium oxide. Both the ethanol and L-carnitine base is molecularly dehydrated and solidified by the reaction of the magnesium cement. Ethanol on its own is also dehydrated in this manner.

Any chemical compound with molecular water may accordingly be dehydrated on a molecular level and be solidified in the manner disclosed herein.

A gas which is soluble in water or in a water containing liquid, may also be entrapped in a solid composition in this manner. The gas may be nitrous oxide. A solution containing water and magnesium chloride may thus be saturated with nitrous oxide. This solution may then be used to make the magnesium (Sorel) cement. The nitrous oxide still present in the water would be entrapped in the solidified cement, and could then be grounded down into a powder to be encapsulated. The entrapped nitrous oxide would only be released once the compound reaches the stomach and is digested by the stomach acid.

It is further part of the applicant's non-binding theory that the mechanism of the process whereby the hydrochloric acid dissolves the composition is as follows:

Two hydrochloric acid molecules reacts with a magnesium oxide molecule to form magnesium chloride and water which in turn is utilized to form magnesium hydrochloride hexahydrate. Water would be taken from the immediate surroundings and the dehydration of the compound would be reversed. The slow release effect of the compound would depend on what the size of the molecule is e.g. $MgCl_2.3MgO.3H_2O$, would take a longer time to dissolve than $MgCl_2.2MgO.4H_20$. The active molecule such as L-carnitine or alcohol or nitrous oxide would be release at the rate at which the dominant molecules of the magnesia cement would be dissolved.

By mixing the compound for a longer period of time more of the $MgCl_2.4MgO.2H_20$ molecules would be present in the compound. The lesser time the compound is mixed the more of the $MgCl_2.3MgO.3H_20$ molecules would be present.

It may also be possible for the molecules to be absorbed as a unit e.g. $MgCl_2.4MgO.2H_20$. The concentrations would be too low to be detected in the serum. A study that was done found that there was increased L-carnitine excretion in the urine at 24 and 36 hours after a bolus dosage of 800 mg in

the composition. The most probable way that this could have been accomplished was that the molecules were absorbed intact and then slowly dissolved in the blood stream.

DESCRIPTION OF PREFERRED FORMULATION AND METHOD OF PRODUCTION:

A quantity representing 0,22 parts by mass of L-carnitine is dissolved in 0,23 parts by mass distilled water. This process must be completed and the resulting solution should be clear before 0,55 parts by mass of magnesium chloride hexahydrate is dissolved in the solution. This process should also be complete and the resulting solution should be clear.

A quantity representing 0,25 parts by mass of magnesium oxide is placed in an open powerful mixer after screening the powder through a sieve. A quantity representing 0,36 parts by mass of the magnesium chloride/L-carnitine/distilled water solution prepared as described above is added to the magnesium oxide while being mixed.

The mixture is initially dry when mixed and becomes a paste after approximately 15 - 20 minutes of mixing.

As soon as the firm paste is formed it is placed in a closed plastic container with a removable lid.

There is a rapid increase of temperature of the paste after 20 - 30 minutes to about 80°C. This reaction takes up to five minutes after which the paste is

set into a hard solid with a mass loss of approximately 5%. A great deal of steam is generated by this reaction and it pushes the lid from the container. Thereafter the dry composition is crushed, for example by means of a finger crusher to 5 mm size, then reduced to 1 mm size, for example by means of a hammer mill, and then reduced to sub-60 micrometer, for example by means of a pindisc mill.

This powder is then fine enough to be encapsulated in a hard gelatine capsule of 769 mg which would contain 254 mg magnesium chloride and 100 mg L-carnitine.

The presence of L-carnitine in the powdery composition could be detected at a mass to charge ratio (m/e) of 161 on a FAB-MS (Fast atomic bombardment mass spectrophotometer). The detection of the L-carnitine was only possible after the compound was treated with a weak solution of methanolic hydrochloride.

This compound needs hydrochloric acid to be dissolved. This is why it would only be dissolved for absorption in the body once it comes in contact with the hydrochloride acid in the stomach.

An analysis of the compound showed other peaks at mass to charge ratio of 244 and 266 this fits in with the following molecules $MgCl_2.2MgO.4H_20$

having a value of 246-2=244, and $MgCl_2.3MgO.3H_20$ having a value of 268 - 2 = 266.

This indicates that different cement molecules were present in the compound. In the stomach these would take different times to dissolve and thus having a slow release effect to release the active molecule such as L-carnitine. It is believed that the following molecules could be present in the Sorel cement composition.

1	$MgCl_2.5MgO.H_20$	amu = 312
2	$MgCl_2.4MgO.2H_20$	amu = 290
3	$MgCl_2.3MgO.3H_20$	amu = 268
4	$MgCl_2.2MgO.4H_20$	amu = 246
5	$MgCl_2.MgO.5H_20$	amu = 224

THE PHARMACEUTICAL APPLICATIONS FOR THE PRODUCTION AND APPLICATION OF THE DIFFERENT COMPOUNDS:

1. **Magnesium chloride / L-carnitine slow release**

A composition comprising dry magnesium chloride and L-carnitine in a hard gelatine capsule is unique. It releases L-carnitine over time for absorption through the stomach and intestine wall when taken orally.

The recommended dosage is one capsule twice a day or 2 capsules in the morning. The indication would be for all conditions requiring supplementary L-carnitine and magnesium administration. This copmposition could also be used to increase the HDL function of cholesterol.

2. **Magnesium chloride / L-carnitine / alcohol slow release**

One capsule containing 254 mg magnesium chloride, 100 mg L-carnitine and 70 mg Ethanol may be produced in the manner as described above. A mass representing 0,22 parts L-carnitine is dissolved in a mass representing 0,23 parts of 86% ethanol. A mass representing 0,55 parts magnesium chloride hexahydrate is added after the first components are dissolved completely.

A mass representing 0,36 parts of this clear solution is added to a mass representing 0,25 parts magnesium oxide while being mixed. The resulting paste is placed in a closed container to contain the evaporation of ethanol. There is no significant increase in temperature after 20 - 30 minutes and the compound takes 2 - 3 days to dry out and to set to a solid mass.

This compound could also be made without the L-carnitine and by using the same mass ratios for the alcohol, magnesium chloride and magnesium oxide a dry slow release compound could be made with magnesia cement and ethanol. The compounds with alcohol could then be used to treat people with alcohol abuse problems seeing that most of those people have a magnesium and L-carnitine deficiency and that this, together with the 70 mg alcohol per capsule, would enable them to stop their drinking habits. The recommended dosage is 2 capsules twice a day for one-week, then 2 capsules per day for 3 months and then 2 placebo capsules per day of the capsules without the alcohol.

This compound could also be used to increase the HDL fraction of cholesterol. It is known the moderate intake of ethanol, magnesium supplement and L-carnitine individually increases HDL cholesterol. This invention provides the means to produce a product that contains all the above mentioned in a single dry composition to be taken orally.

3. **Magnesium chloride / L-carnitine / nitrous oxide slow release**

A mass representing 0,22 parts L-carnitine is dissolved in a mass representing 0,23 parts distilled water. A mass representing 0,55

parts magnesium chloride hexahydrate is added to dissolve completely. This solution is saturated by nitrous oxide gas by using pressure. A mass representing 0,36 parts of this solution is added to a mass ratio of 0,25 magnesium oxide and mixed. The resulting paste is placed in a closed container to dry while preventing the escape of the gas. The dried composition is then grounded down.

An indication for use of this compound would be for the oral treatment of HIV infection, viral infections, gout, psoriasis, cancer, rheumatism, hypercholesterol, alcoholism and osteoporosis.

The compound could also be used for its anti-inflammatory action against viral infections in animals and birds including ostriches. It could also be used as an anti-inflammatory in allergic reactions or in cases of an overactive immune system.

4. **Magnesium chloride/nitric oxide slow release**

A mass representing 0,55 parts of magnesium chloride hexahydrate is dissolved completely in a mass representing 0,23 parts distilled water. This solution is saturated by nitric oxide gas by making use of pressure. A mass representing 0,36 parts of this solution is added to a mass representing 0,25 parts magnesium oxide. The resulting paste

is placed in a closed plastic container to dry. The dried compound is then grounded down. The indications of this compound is the same as the magnesium L-carnitine/nitrous oxide compound.

5. **Magnesium chloride / L-carnitine / nitric oxide slow release and Magnesium chloride/nitrous oxide slow release**

This process and ratios is the same as the process for nitrous and nitric oxide compositions numbers three and four above. Care must be taken however, particularly in the case of nitric acid formulations to use deoxygenated water and the mixing should take place in an enclosed environment to minimize the inclusion of oxygen in the compound so that nitric acid formation could be minimized or excluded.

6. **Magnesium / pantothenic acid slow release**

A mass representing 0,22 parts pantetonate is dissolved in a mass representing 0,23 parts distilled water. A mass representing 0,55 parts magnesium chloride hexahydrate is added to dissolve completely. A mass representing 0,36 parts of this solution is mixed with a solution of a mass representing 0,25 parts magnesium oxide. The resulting paste is placed in a container to dry. The dried

compound is then grounded down and encapsulated. It is used in any application wherein the supplementation of diet by pantetonate is indicated.

7. General molecular dehydration of hygroscopic substances

The mass representing 0,22 parts of the substance to be "dehydrated" and which is to be dissolved in distilled water with a mass representing 0,23 parts of H_2O is to be used for the total of one or more of the substances to be added. If necessary the distilled water could be rendered more alkaline by adding a mass representing 0,006 sodium hydroxide. In this regard it is desirable to adjust the pH of the aqueous solution of the substance to be entrapped to a value below 7, and preferably to a value between 7 and 9 before addition of the magnesium chloride thereto. A mass representing 0,55 parts magnesium chloride hexahydrate is then used to complete the solution. A mass representing 0,36 parts of this solution is thereupon added to a mass representing 0,25 parts of dry powdery Magnesium Oxide as a general rule, which rule may require refinement in certain circumstances.

Countless variations of the invention may be devised without departing from the spirit of the invention which may also in particular be applied in the formulation of compositions containing any of the following ingredients:

acetylcarnitine; creatine and derivatives; Vitamin F oil; ostrich oil; fat soluble vitamins such as Vitamin A and derivatives thereof or Vitamin E (dl-tocopherol); steroids; hormones, e.g. estrogen and testosterone; plant extracts including oils, water soluble fractions and ethanolic extractions; nicotinamide adenine dinucleotide (NAD); and fluorine gases such as halothane and the like.

CLAIMS:

1. A solid dosage form of a pharmaceutically active substance selected from the group consisting of pharmaceutically active water soluble gaseous substances, ethyl alcohol, L-carnitine, pantothenic acid, pyruvate, and combinations thereof, comprising a magnesium oxychloride cement (also known as a Sorel cement) in which the pharmaceutically active substance is entrapped.

2. The solid dosage form of claim 1 in which the cement is in the form of a powder packed in a capsule.

3. The solid dosage form of claim 1 in which the cement is in a compressed tablet form.

4. The solid dosage form of claim 1 in which the magnesium oxychloride cement is made up by mixing a clear magnesium chloride solution containing the pharmaceutically active substance with magnesium oxide powder to form a paste which is then allowed to set over time into a solid composition which composition is then optionally crushed and milled to the desired fineness.

AA-37

5. The solid dosage form of any one of claims 1 to 4 wherein the entrapped pharmaceutically active substance is or includes nitrous oxide.

6. A method of producing a solid dosage form of a pharmaceutically active compound comprising the steps of forming a clear basic aqueous solution of the compound, dissolving magnesium chloride hexahydrate into that solution and using the resultant solution to form magnesium oxide powder into a paste, allowing the paste to set into a solid composition and, if desired, grinding the set composition into a powder.

7 The method of claim 6 wherein the pharmaceutically active compound is selected from the group consisting of pharmaceutically active water soluble gaseous substances, ethyl alcohol, L-carnitine, pantothenic acid, pyruvate, and combinations thereof.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

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(54) Title: A SLOW RELEASE PHARMACEUTICAL COMPOSITION

(57) Abstract: The invention relates to slow release pharmaceutical compositions. More particularly it relates to the combination of hygroscopic solid, liquid or gaseous pharmaceutically active substances with solidifying materials of the type known as Sorel cement thereby to produce solid compositions which, when taken orally, has slow releasing properties in respect of the substance so incorporated into the composition.

COMBINED DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
(Page 1)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

A SLOW RELEASE PHARMACEUTICAL COMPOSITION

the specification of which [X] was filed on March 29, 2002 as United States Application No. 10/089,439 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b), of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designates at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed:

Country	Application No.	Filed (Day/Mo./Yr.)	(Yes/No) Priority Claimed
South Africa	99/6190	September 29, 1999	Yes
PCT	PCT/ZA00/00180	September 29, 2000	Yes

I hereby appoint the practitioners associated with the firm and Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to the address associated with that Customer Number:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Sole or First Inventor Henry John Davis

Inventor's signature _____

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